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| EXAMINER | |
|---|---|
| KISHORE, GOLLAMUDI S | |

| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/748,094 | DAFTARY ET AL. | |
| | Examiner | Art Unit | |
| | Gollamudi S. Kishore, Ph.D | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-8,10-22,61 and 62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-22,61 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The RCE dated 10-31-07 is acknowledged.

Claims included in the prosecution are 1-8, 10-22 and 61-62.

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 61 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to claim 1, hydration is performed after making the lipid film; claim 61 which recites a further step of removing the solvent before or after hydrating the lipid film is inconsistent with claim 1.

### *Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-8, 10-22 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin (6,110,491).

Kirpotin discloses a method of preparation of liposomes by forming a lipid film

and hydrating it with a buffer containing ammonium sulfate (Example 7). Kirpotin also teaches that if necessary, to achieve an osmolarity of 377 mmole/kg, sucrose could be added to the medium (Example 8). The liposomes contain hydrogenated egg phospholipid and cholesterol. Doxorubicin is loaded into the preformed liposomes (Example 7). Although in the examples Kirpotin uses PEG-phospholipids, on col. 9, lines 22-33 teaches either the naturally occurring or synthetic phospholipids which implies that the use of PEG-phospholipids for the method of preparation of liposomes is not necessary. What is lacking in Kirpotin is the teaching of the amount of aqueous medium added to per mol phospholipid. However, since the final product in Kirpotin is a liposome just as in instant case, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts of the hydrating medium to obtain the best possible results.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Kirpotin does not teach or suggest a process for the manufacture of long circulating non-PEGylated liposomes as set forth in claim 1 and that the examiner has offered no factual evidence to support his statement that Kirpotin teaches or suggests non-PEGylated liposomes. This argument is not persuasive since as pointed out above, although in the examples Kirpotin uses PEG-phospholipids, on col. 9, lines 22-33 teaches either the naturally occurring or synthetic phospholipids which implies that the use of PEG-phospholipids for the method of preparation of liposomes is not necessary. Applicant further argues based on the declaration by MR. Annappa that instant invention provides unexpected results compared to the PEGylated liposomal

preparation (CAELYX) marketed currently. These arguments are not persuasive since the proper comparison to show unexpected results would be the comparison with Kirpotin and not with the commercially available PEGylated product since this product was not used in the rejection. Instant claims recite a process of preparation of liposomes containing phospholipids and sterol, which are not PEGylated and Kirpotin, teaches the preparation of non-PEGylated liposomes.

5. Claims 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin (6,110,491) in view of Emanuel (US 2002/0151508).

The teachings of Kirpotin have been discussed above. What is lacking in Kirpotin is the use of sucrose- histidine buffer. The use of this buffer however, would have been obvious to one of ordinary skill in the art with the expectation of obtaining similar results since the reference of Emanuel shows its routine use in the preparation of liposomes (0033 and claims 4 and 5).

6. Claims 1-8, 10-22 and 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forssen (5,714,163) in combination with Janoff (4,880,635).

Forssen discloses a method of preparation of liposomes wherein the lipid film is hydrated with ammonium sulfate. The liposomes contain DSPC and cholesterol and vincristine. Vincristine is added to the preformed liposomes (Example 1) Although Forssen teaches the use of 300 mM sucrose, he does not teach the use of hydration buffer containing both ammonium sulfate and sucrose

Janoff teaches that sugars such as sucrose when present both inside and outside would enable the liposomes to retain Adriamycin during dehydration and rehydration (col. 21, line 23 through col. 21, line 27). Janoff further teaches the hydration of the 80 micromoles of lipid with 2 ml of buffer (25 ml per mmole).

To include sucrose in the hydration medium of Forssen would have been obvious to one of ordinary skill in the art since such a procedure would enable the presence of sucrose within the liposomes as well as outside and since Janoff teaches that the liposomes retain the active agent during dehydration and rehydration procedures. Although Forssen does not specifically teach the amount of aqueous medium added per mol phospholipids, since the final product in Forssen is a liposome just as in instant case, and since the bilayer formation is a result of the complete hydration of the phospholipid, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts of the hydrating medium to obtain the best possible results. One of ordinary skill in the art would be motivated to use claimed amounts of aqueous medium with the expectation of obtaining similar results since Janoff teaches such a hydration amount. The criticality of the histidine buffer in claim 62 is not readily apparent to the examiner in the absence of comparative studies.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that one skilled in the art would not be motivated to even consider Forssen or Janoff for suggesting a nonpegylated liposome made by reducing the amount of hydration buffer. This argument is not persuasive since the formation of a bilayer occurs only when the lipid film is hydrated fully and applicant has not shown

through studies that the claimed amounts of hydration buffer are critical. In addition, Janoff teaches instant amounts. Furthermore, whether the liposome has a long circulation also depends upon the type of phospholipid used. Applicant has not shown that because of these hydration buffer amounts, the liposomes have the longer circulating times. The examiner cites the references of Maruyama (International Journal of Pharmaceutics) and that of Park which teaches liposome made of some negatively charged phospholipids prolong the circulation time. Applicant's arguments that Janoff teaches liposomes that are required to be dehydrated and then rehydrated to achieve long term storage are not persuasive since Janoff first of all teaches the inclusion of sugar in the hydration buffer as evident from col. 8, lines 40-43. Secondly, Janoff is combined for this teaching alone and instant 'comprising' does not exclude further dehydration and rehydration of the liposomes. teaches liposomes which Applicant's arguments once again are based on the declaration by Mr. Annappa to show unexpected results. As pointed out above, since the rejection is based on the Forssen and Janoff and not based on the commercially available product CAELYX, the proper comparison would be with the applied prior art teachings. The rejection therefore, is maintained.

7. Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Forssen (5,714,163) in combination with Janoff (4,880,635) as set forth above, further in view of Emanuel (US 2002/0151508).

The teachings of Forssen and Janoff have been discussed above. What is lacking in these references is the use of sucrose- histidine buffer. The use of this buffer

however, would have been obvious to one of ordinary skill in the art with the expectation of obtaining similar results since the reference of Emanuel shows its routine use in the preparation of liposomes (0033 and claims 4 and 5).

8. Claims 1-8, 10-22 and 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forssen (5,714,163) in combination with Janoff (4,880,635) as set forth above, further in view of Radhakrishnan (5,192,528) or Uchiyama (International Journal of Pharmaceutics, 1995).

The teachings of Forssen and Janoff have been discussed above. As pointed out above, Forssen does not teach the hydration buffer amount to be 10 to 35 ml per mmole of the phospholipid.

Radhakrishnan while disclosing corticosteroid containing liposomes teaches that the aqueous medium is added to a final lipid concentration of between about 10 to 100 micromole/ml which translates to 100 to 10 ml per mmole phospholipid (abstract and col. 5, lines 15-29).

Uchiyama while disclosing a method of preparation of liposomes containing EPC, HEPC, DCP and cholesterol teaches the hydration of 200 micromoles of lipids using 5 ml of aqueous medium, which translates to 1 mmole lipid and 25 ml of aqueous medium (Materials and methods, liposome preparation).

It would have been obvious to one of ordinary skill in the art to use claimed amounts of the hydration medium to hydrate the lipid of Forssen since the references of Radhakrishnan and Uchiyama teach that these are typical amounts of the hydration medium.

9. Claims 1-8, 10-22 and 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong (Clinical Cancer Research, 1999) of record in view of Janoff cited above and either Radhakrishnan (5,192,528) or Uchiyama cited above.

Hong teaches a method of preparation of doxorubicin loaded liposomes. The method involves hydration of the lipids using ammonium sulfate solution (abstract and Materials and Methods). What is lacking in Hong is the use of sucrose in the hydration buffer. It is unclear from Hong as to how much hydration buffer is added.

Janoff teaches that sugars such as sucrose when present both inside and outside would enable the liposomes to retain Adriamycin during dehydration and rehydration (col. 21, line 23 through col. 21, line 27). Janoff further teaches the hydration of the 80 micromoles of lipid with 2 ml of buffer (25 ml per mmole).

Radhakrishnan while disclosing corticosteroid containing liposomes teaches that the aqueous medium is added to a final lipid concentration of between about 10 to 100 micromole/ml which translates to 100 to 10 ml per mmole phospholipid (abstract and col. 5, lines 15-29).

Uchiyama while disclosing a method of preparation of liposomes containing EPC, HEPC, DCP and cholesterol teaches the hydration of 200 micromoles of lipids using 5 ml of aqueous medium, which translates to 1 mmole lipid and 25 ml of aqueous medium (Materials and methods, liposome preparation).

To include sucrose in the hydration medium of Forssen would have been obvious to one of ordinary skill in the art since such a procedure would enable the presence of

sucrose within the liposomes as well as outside and since Janoff teaches that the liposomes retain the active agent during dehydration and rehydration procedures. It would have been obvious to one of ordinary skill in the art to use claimed amounts of the hydration medium to hydrate the lipid of Forssen since the references of Radhakrishnan and Uchiyama teach that these are typical amounts of the hydration medium.

10. Claim 62 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hong (Clinical Cancer Research, 1999) of record in view of Janoff cited above and either Radhakrishnan (5,192,528) or Uchiyama cited above, further in view of Emanuel (US 2002/0151508).

The teachings of Hong, Janoff and Radhakrishnan have been discussed above. What is lacking in these references is the use of sucrose- histidine buffer. The use of this buffer however, would have been obvious to one of ordinary skill in the art with the expectation of obtaining similar results since the reference of Emanuel shows its routine use in the preparation of liposomes (0033 and claims 4 and 5).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G Kishore/

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1612

GSK